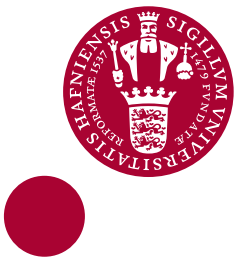

Caught in the act: multiple binding sites for memantine

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Caught in the Act: Multiple Binding Sites for Memantine

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In this issue of *Structure*, Ulens and colleagues demonstrate how an elegant combination of complementary functional and structural approaches can uncover both binding sites and conformational consequences associated with the Alzheimer's drug memantine binding to an ion channel.

A hallmark of neuronal activity is the fascinating ability of neurons to exchange information with remarkable speed and precision. Nowhere is this better illustrated than at the synapse, the cellular equivalent of a relay station. The presynaptic cell is faced with the daunting challenge to communicate urgent news, i.e., the arrival of an action potential to its neighbor, the postsynaptic cell. The predominant solution to bridge the void between the cells, the so-called synaptic cleft, is by way of electrically induced neurotransmitter release by the presynaptic cell. This conversion from an electrical to a chemical signal is immediately reversed again when the neurotransmitter, after traveling across the cleft, binds to its target receptor in the postsynaptic membrane. This triggers the opening of a pore within the receptor, resulting in ionic flux across the postsynaptic membrane and therefore in a change of the electrical excitability of the postsynaptic cell.

Understanding this intricate process has not only posed a formidable challenge for decades, but its pharmacological modulation forms a potent means of rectifying pathophysiological neuronal activity. This is particularly true for the above postsynaptic receptors, a large class of ion channels including the pentameric ligand-gated ion channels (pLGICs). Neurotransmitter binding to the pLGIC extracellular ligand-binding domain (LBD) is thought to trigger a series of conformational changes that subsequently open the channel pore in the transmembrane domain (TMD) (Figure 1). Given their central role in fast synaptic transmission and the ever increasing number of disease states associated with these receptors, it is not surprising that pLGICs are the target of numerous clinically relevant drugs that can initiate, modulate, or block their activity.

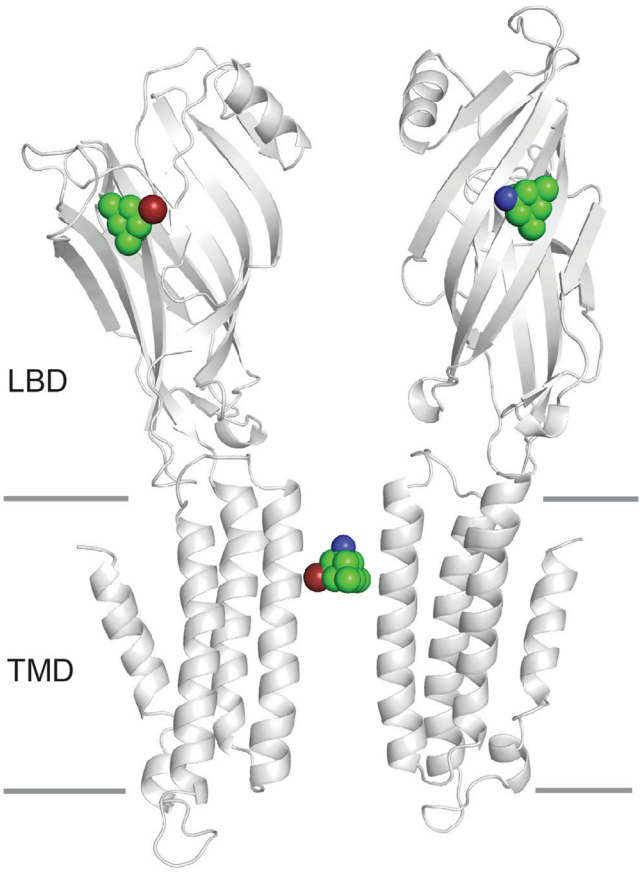

Figure 1. ELIC F16'S Bound to Br-Memantine: 4TWH
Only two of the five ELIC subunits are shown for clarity. Three Br-memantine molecules are shown to highlight their simultaneous occupancy of the channel pore in the TMD as well as the orthosteric binding sites in the LBD.

One such therapeutic, memantine, is clinically used for the management of Alzheimer's disease symptoms. It is believed that memantine elicits its function by inhibiting ligand-gated ion channels. However, the molecular details of how drug binding results in the functional inhibition remained enigmatic. In this issue of *Structure*, Ulens et al. (2014) present the X-ray crystal structure of ELIC, a prokaryotic pLGIC, in the presence and absence of memantine, providing the first example of a closed pLGIC pore in a blocker-bound conformation. Intriguingly, the data suggest that memantine not only binds in the upper half of the TMD, thereby exerting its blocking effect, but also that memantine binds in the orthosteric ligand-binding pocket in the LBD, a site usually highly selective in the recognition of the cognate neurotransmitter. While the identification of more than one binding site for a small molecule modulator or inhibitor may not come as a big surprise (Hamouda et al., 2014), it is

fascinating to see that the molecule in question is able to show up in the two most sacred spots of the receptor: its pore and its orthosteric binding site. This constitutes an interesting complement to the often complex effects of channel blockers on pLGICs observed in functional electrophysiology experiments, which was also found by the authors in the case of memantine and ELIC. In fact, this may not be dissimilar from the finding that nicotinic acetycholine receptors are both activated and (at higher concentrations) blocked by a range of ligands (Sine and Steinbach, 1984). The current study therefore sheds new structural light on this long-standing observation and may well trigger renewed interest in this fascinating phenomenon.

The pLGIC field has greatly benefitted from a recent surge in available crystal structures, first by bacterial pLGIC homologs (reviewed in Corringer et al., 2012) and later followed by eukaryotic pLGICs (Althoff et al., 2014; Hassaine et al., 2014; Hibbs and Gouaux, 2011; Miller and Aricescu, 2014). The present study therefore adds to an already astounding number of crystallographically observed pore conformations among pLGICs. However, the authors also point out an intriguing twist in the story; although the structurally determined closed pore conformation is uncannily similar under memantine-free and memantine-bound conditions, their data from combined electrophysiological and fluorescence measurements suggest that memantine induces a conformational state distinct from that of the agonist-free (and likely also the agonist-bound) receptor. This is an important finding, because it suggests that the entire conformational landscape visited by the protein in an intact membrane may, in some cases, lie beyond the grasp of X-ray crystal structures. Interestingly, this is in good agreement with another recent crystallography study on ELIC, in which the authors found that significant functional changes failed to translate into crystallographically observable structural changes of the protein (Gonzalez-Gutierrez et al., 2012).

It will be fascinating to see what combinations of structural and functional approaches eventually uncover the whole range of conformational states and transitions in pLGICs and other ion channels.

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Switch for the Necroptotic Permeation Pore

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The helical protein MLKL inserts into cell membranes and forms a permeation pore therein, resulting in cell death. In this issue of *Structure*, the article by Su and colleagues reports that helix 6 regulates the opening of the pore formed by preceding core helices.

Under disease-induced stress, cells launch a suicide protocol that activates formation of a permeation pore in the cell membrane. The pore is formed by the MLKL protein and allows osmotic swelling and rupture, ultimately leading to cell death. This process is called necroptosis, an emerging form of programmed cell deaths, which is different from its well-known rhyming cousin apoptosis (Sun et al., 2012; Wang et al., 2014). In this issue of *Structure*, the article by Su et al. (2014) provides critical insights into how MLKL forms the pore in the membrane and, more importantly, how the pore is regulated at a molecular level.

MLKL belongs to a class of proteins that are expressed as soluble polypeptides but insert into the membrane to form permeation pores or channels. They include bacterial toxins such as colicin and diphtheria toxin as well as the Bak/Bax proteins, which play an essential role in apotosis. In MLKL, the N-terminal membrane binding domain (MBD) is connected to the C-terminal regulatory domain, whose phosphorylation status regulates the opening of the pore (Su et al., 2014; Wang et al., 2014).

Using nuclear magnetic resonance (NMR) spectroscopy, Su et al. (2014) found